UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,242	05/24/2005	Ashok Venkitaraman	BJS-620-363	7844

23117 7590 07/02/2007
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
07/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,242	VENKITARAMAN ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-36* is/are pending in the application.

4a) Of the above claim(s) *26-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :04/14/2005, 11/02/2006, 11/03/2006.
Continuation of Attachment(s) 6). Other: Notice to comply, PDB of 1nOw, NCBI of P42212, NCBI of CAA64484, NCBI of AAA43099.

DETAILED ACTION

Application Status

1. By virtue of a preliminary amendment filed on 04/14/2005, Claims 1-19 have been canceled; and Claims 20-36 have been added. Thus, Claims 20-36 are pending in this instant case.

Election

2. Applicant's election with traverse of Group I, (Claims 20-25) in the reply filed on 04/09/2007 is acknowledged. The traversal is on the ground(s) that the Examiner has not established lack of unity by citing an anticipatory prior art and the Office has not shown that an undue burden exists in searching the entire application. This is not found persuasive because each Group represents a distinct independent invention and do not require the special technical feature of polypeptide of Group I. Also, the search burden exist by the virtue of different class and subclass between distinct inventions and the search for each Group requires different key words because divergent subject matters on application. Searching altogether would create serious search burden on the examination. The election requirement is still deemed proper and is therefore made FINAL.

Claims 21-36 are pending in the instant application. Claims 26-36 are withdrawn from consideration as non-elected inventions. Thus, Claims 20-25 will be examined herein.

Priority

3. The instant application is a 371 filing of the International Application No. PCT/GB03/04485 filed on 10/14/2003. The Examiner notes that the requirements of national stage entry of the instant application have been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date.

4. Acknowledgment is made of applicant's claim for foreign priority based on a foreign patent application 0223860.8 (United Kingdom) filed on 10/14/2002. It is noted, however, that applicant has not filed a certified copy of the said foreign application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

5. The information disclosure statements (IDSs) filed on 04/14/2005, 11/02/2006, 11/03/2006 have been reviewed, and the references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the

final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) The structural coordinates in Figure 1 teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling all contiguous amino acids using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly. The SEQ ID NO: 1 and SEQ ID NO: 2 disclosed in the amended specification page 2 (filed on 01/03/2007) does not disclose correct SEQ ID NO(s). Appropriate correction is required.

b) The Figure 3 discloses two polypeptide without appropriate SEQ ID NOs. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly. Appropriate correction is required.

c) The Figure 7 (d) discloses polypeptides without appropriate SEQ. ID NOs. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly. Appropriate correction is required.

d) The polypeptide of FHTA on page 5, line11, requires appropriate SEQ ID NO. Appropriate correction is required.

e) The polypeptide of "(ThrGlySer)4MetGly" on page 32, line2, requires appropriate SEQ ID NO. Appropriate correction is required.

f) The sequence listing has many names other than the instant inventors on the first page. It is unclear why these names appear on the instant sequence listing. Appropriate clarification is required.

g) The statement that the content of the paper and CRF copies are the same is missing.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

7. The specification is objected to because of the following informalities:

a) The specification is objected to because the title is not descriptive of the claims. A new title is required that is clearly indicative of the invention to which the claims are drawn (see M.P.E.P. § 606.01). The examiner suggests the following new title, for example: ---A crystal of a RAD51-BRC repeat sequence complex---

b) The Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the name of the source of protein for completeness.

c) In view of the PCT/GB2003/004485, there are 7 inventors. The inventorship of the instant application have only five. Appropriate clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 22 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The phrases "a resolution of better than 2.0" Angstroms in claim 22 is unclear as to the limitations they impart on the claimed subject matter or as to what said phrases encompass and one of ordinary skill in the art would not be reasonably apprised of the scope of the claimed crystals. It is well known in the art that the smaller the number (i.e. Angstroms), the higher the resolution. In this case, the term can be interpreted in the

following two distinct ways: 1) a resolution of a number greater than 2.0 Å, which is a lower resolution or 2) a resolution of a number less than 2.0 Å, which is a higher resolution. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 20-25 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to any crystal of a RAD51-BRC repeat sequence complex with optional additional limitations presented in individual, dependent claim form such as: having orthorhombic space group $P2_12_12_1$ and unit cell dimensions a=57.30 ± 5%, b=59.14 ± 5%, c=77.20 ± 5% (Claim 21); having a resolution of better than 2.0 Å (Claim 22); having three dimensional atomic coordinates of Table 1 (Claim 23). Claim 24 and 25 is drawn to a "RAD51-BRC repeat sequence chimaera protein" or "RAD51 prologue-BRC repeat sequence chimaera protein" which encompass a protein in both solution as well as the crystal of said protein, given the protein crystal also have the same amino acid residues as protein in a solution.

Based on the term "complex" in claim 20, "chimaera protein" in Claim 24 or "paralogue" in Claim 25, which have been interpreted as the terms that open up the limitation (which is similar to the term "comprising") of the instant claimed crystal or said proteins wherein the recited terms are not defined by the instant specification. For example, any complex or fusion product (both in solution and crystalline form) as long as the complex has the RAD51-BRC repeat sequence, or RAD51 homolog or variant with BRC repeat sequence are encompassed by the Claim 20, 24 or 25.

While the structure and function of one species of said genera of a crystal of RAD51-BRC repeat sequence complex are disclosed in the specification, the common structural characteristics of species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

Although, Example I. 2. on page 32 describes the crystallization of RAD51-BRCA2 BRC4 complex (without identifying a SEQ ID NO) in the absence of ligands, the specification describes one species of a RAD51-BRC repeat sequence complex crystal that falls within the instant genera of crystal. The crystal form described by Figure 7 is within the genera of Claims 20-25 based on their sequence, space group symmetry, unit cell dimensions (including error), and resolution.

While the claim language requires a function for the instant genera of crystals (that of RAD51-BRC), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately structurally described, the following must be adequately disclosed: (1) the composition of the crystal [exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it], (2) the space group, and (3) the unit cell dimensions of the crystal.

The species noted above has adequately met this burden by the description in the instant specification. However, the composition of the crystals encompassed by the breadth of the claims is not described because the exact molecule is not limited nor the space group and unit cell dimensions associated with this breadth of chemical composition described. In Claim 21, only space group and unit cell dimensions are adequately described. It is noted, the exact polypeptide sequence (unknown SEQ ID

NO), with any ligands in Claims (if any), accompanied by the word "comprises" does not disclose the exact composition of the protein crystal in Claims 3 and 8. The space group and unit cell dimension disclosed in Claim 22 satisfies two adequate description but missing the other one descriptions as noted above. A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the disclosed species of the instant disclosure. Therefore, claims drawn to the instant genera of crystals are also not adequately described.

9. Claims 20-26 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method for preparing a protein crystal of the RAD51-BRC repeat sequence polypeptide consisting of the inherent sequence as the protein used to form a crystal described by the Figure 1 (without SEQ ID NO in the instant application) that results in a crystal having the space group $P2_12_12_1$ and the unit cell dimensions a=57.30 ± 5%, b=59.14 ± 5%, c=77.20 ± 5%, does not reasonably provide enablement for all crystals as broadly encompassed by the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The breadth of the claims: Claim 20 (Claims 21-23 dependent therefrom) is so broad as to encompass any protein crystals of any RAD51-BRC repeat sequence with

unlimited amino acid sequence. Claims 21 is so broad as to encompass any protein crystal as long as the crystal has the space group $P2_12_12_1$ and the unit cell dimensions a=57.30 ± 5%, b=59.14 ± 5%, c=77.20 ± 5%. Claim 22 is so broad as to encompass any protein crystals of any RAD51-BRC repeat sequence with unlimited amino acid sequence as long as the crystal has a resolution of better than 2.0 Angstroms. As noted above, based on broad and reasonable interpretation, the term "complex" in claim 20, "chimaera protein" in Claim 24 or "paralogue" in Claim 25 have been interpreted as the terms that open up the limitation of the instant claimed crystal or said proteins wherein the recited terms are not defined by the instant specification. For example, any complex or fusion product (both in solution and crystalline form) as long as the complex has the RAD51-BRC repeat sequence, or RAD51 homolog or variant with BRC repeat sequence are encompassed by the Claim 20, 24 or 25.

The nature of the invention: The invention is related to protein crystals of RAD51 covalently bound to a BRC repeat sequence, which is expressed in E. *coli* with His tag which is cleaved by TEV protease as described in the top of page 32 of the specification wherein the crystal consists of the inherent sequence as the protein used to form a crystal described by the Figure 1 (without SEQ ID NO in the instant application) that results in a crystal having the space group $P2_12_12_1$ and the unit cell dimensions a=57.30 ± 5%, b=59.14 ± 5%, c=77.20 ± 5%. At the time of the invention, methods of protein crystallization were well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the

conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the claimed crystals, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals... are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, *Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be

empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., who teach the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Along these same lines, Wiencek (*Ann Rev Biomed Eng,* 1999, 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of any other RAD51-BRC repeat sequence can be achieved using the crystallization parameters as set forth at p. 32 of the specification. Alternatively, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of any protein encompassed by the instant claims can be achieved using any crystallization parameters. Furthermore, the resolution "better than 3.0" Angstroms as disclosed in Claim 23 is not possible to predict by one skilled in the art because the resolution must be determined by X-ray crystallography.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only a single working example of the claimed

crystal and the method of crystallization thereof. See specification at pp. 32. In Pellegrini et al. (21 November 2002, Nature, vol. 420, pages 287-293), the RAD51-BRC fusion protein is known in the art within the scope of instant Claims. Other than these **two** working examples, the specification fails to provide guidance for altering the crystallization conditions for crystallizing any other polypeptide comprising RAD51-BRC, any RAD51-BRC complexed with any other protein or any protein or protein crystal comprising variants of RAD51-BRC with an expectation of obtaining diffraction-quality crystals. Further, the specification fails to provide guidance for crystallizing the protein used in the instant example on page 32 with other ligands or any other conditions with an expectation of obtaining diffraction-quality crystals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of setting up a protein crystallization were known at the time of the invention, these methods are specific to a particular protein as evidenced by the above teachings. Thus, a skilled artisan is left to experiment by a trial and error process to determine whether the disclosed crystallization conditions can be applied to a crystallization of other proteins, encompassed by a very widely varying genus, can be crystallized under a different set of crystallization parameters.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be

necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 24-25 are rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. Claims 24-25, as written, does not sufficiently distinguish over cells as they naturally exist because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended

to indicate the hand of the inventor, e.g. by insertion of "isolated" or "purified" as taught by the specification. See M.P.E.P. § 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 20-25 are rejected under 35 U.S.C. 102(a) as being anticipated by Pellegrini et al. (21 November 2002, Nature, vol. 420, pages 287-293, as cited in the IDS).

As noted above in the instant office action, the term "complex" in claim 20, "chimaera protein" in Claim 24 or "paralogue" in Claim 25 have been interpreted as the terms that open up the limitation (which is similar to the term "comprising") of the instant claimed crystal or said proteins wherein the recited terms are not defined by the instant specification. For example, any complex or fusion product (both in solution and crystalline form) as long as the complex has the RAD51-BRC repeat sequence, or RAD51 homolog or variant with BRC repeat sequence are encompassed by the Claim 20, 24 or 25.

Pellegrini et al. teach a crystal of RAD51-BRCA2 complex as shown in Figure 1, page 288. The crystal have a space group $P2_12_12_1$ and unit cell dimensions of

a=57.30, b=59.14, c=77.20 with a resolution of 1.70 Angstroms (see PDB data of 1nOw). Pellegrini et al. "covalently linked BRC4 to RAD51" for the fusion protein (see top of right column, page 287). The coordinates of Table 1, which are processed using a series of processing steps using a known algorithm, do not appear to impose a change in the processing steps or functioning of the computer and there is no evidence of record that the data of Table 1 imposes a change in the function of the computer. Put another way, the function of the computer is the same whether the computer comprises the data of Table 1 or not. Thus, all claim limitations concerning the structure coordinate data of Table 1 are given no patentable weight as the data is considered to be non-functional descriptive material. Thus, the crystal of Pellegrini et al. meet the limitations of Claims 20-25.

11. Claim 24 rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (2002, Nucleic Acids Research, vol. 30, pages 1009-1015).

Liu et al. teach HeLaS3 cells transfected with plasmid pDS179, "which expresses the human Rad51D cDNA tagged at the N-terminus with an epitope of influenza hemagglutinin (HA)" (see bottom of right column, p. 1010). The expressed Rad51D tagged with HA (HA-Rad51D) by covalent bond is encompassed by a RAD51-BRC repeat sequence chimaera protein or RAD51 paralogue-BRC repeat sequence chimaera protein. The HA protein of Liu et al. is encompasses by the recited "BRC repeat sequence" because the dipeptide IleIle in the BRCA2, which is repeated through out the BRCA2 protein, is in the HA protein in view of NCBI AAA43099 and NCBI

CAA64484 (in the attachment) for the protein sequences of HA and braca2. Thus, the HA-Rad51D of Liu et al. meets the limitation of a protein comprising RAD51 covalently joined to BRC repeated sequence, wherein the fusion protein of HA-Rad51D is encompassed by the recited "chimaera protein" in Claim 24.

12. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Yuan et al. (1999, Cancer Research, vol. 59, pages 3547-3551).

Yuan et al. teach an expression of BRC-GFP. The BRC-GFP has a covalent bond because the protein was expressed from a gene "in-frame fusion of GFP to the BRC" (see top of right column, page 3548), which meets the limitation of being chimaera protein by covalent bond. As noted above in 112 1st paragraph, interpretation of recited term "paralogue", the GFP of Yuan et al in the fusion protein (i.e., chimaera protein) is encompassed by the recited term paralogue in Claim 25. The GFP protein of Liu et al. is encompasses by the recited "BRC repeat sequence" because the dipeptide LeuLeu in the BRCA2, which is repeated in the BRCA2 protein, is in the GFP protein, evidenced by NCBI P42212 and NCBI CAA64484 (in the attachment) for the protein sequences of GFP and braca2. Thus, the BRC-GFP meets the limitations of Claim 25.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
November 16, 2006

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER

Notice to Comply	Application No. 10/531,242	Applicant(s) Venkitaraman et al.	
	Examiner Alexander Kim	Art Unit 1656	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See next page.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

7. cont.

The structural coordinates in Figure 1 teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling all contiguous amino acids using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly. The SEQ ID NO: 1 and SEQ ID NO: 2 disclosed in the amended specification page 2 (filed on 01/03/2007) does not disclose correct SEQ ID NO(s).

The Figure 3 discloses two polypeptide without appropriate SEQ. ID NO. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

The Figure 7 (d) discloses polypeptide without appropriate SEQ. ID NO. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

The polypeptide of "FHTA" on page 5, line11, require appropriate SEQ ID NO.

The polypeptide of "(ThrGlySer)4MetGly" on page 32, line2, requires appropriate SEQ ID NO.

The sequence listing has many names other than the instant inventors on the first page. It is unclear why these names appear on the instant sequence listing.

The statement that the content of the paper and CRF copies are the same is missing.